

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|---|
| Applicant's or agent's file reference 99/08168 WO | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/EP 99/ 03838 | International filing date (day/month/year) 02/06/1999 | (Earliest) Priority Date (day/month/year) |
| Applicant MEDINOVA MEDICAL CONSULTING GMBH | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 03838

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 12-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/03838

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/51 A61K31/70 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | WO 95 22963 A (MEDINOVA MED CONSULTING GMBH) 31 August 1995 (1995-08-31) cited in the application the whole document in particular: page 6, line 10 -page 7 page 13, line 9 - line 11 ---- | 1-14 |
| X | WO 98 56361 A (MEDINOVA MED CONSULTING GMBH ;SABEL BERNHARD A (DE); SCHROEDER ULR) 17 December 1998 (1998-12-17) cited in the application the whole document in particular: page 5, line 20 -page 9, line 5 page 15, line 1 - line 3 ----- -/-- | 1-14 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

15 February 2000

Date of mailing of the international search report

24/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Epskamp, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/03838

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | DE 197 45 950 A (DDS DRUG DELIVERY SERVICE GES) 22 April 1999 (1999-04-22) page 3, line 27 -page 4, line 9 page 5, line 40 - line 45; examples 2,6; table 1 page 9, line 10 - line 26 claims 1-20 | 1-14 |
| X | RESZKA R, ET AL.: "Body distribution of free, liposomal and nanoparticle-associated mitoxantrone in B16-melanoma-bearing mice" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, 'Online! vol. 280, no. 1, 1997, pages 232-237, XP002129865 ISSN 0022-3565 Retrieved from the Internet: <URL:http://jpet.aspetjournals.org/cgi/rep rint/280/1/232> 'retrieved on 2000-02-07! page 233, line 31 - line 49 page 233, line 57 -page 234, line 21 page 236, line 12 - line 27; figures 1-6; table 1 | 1,3-13 |
| X | US 5 133 908 A (STAINMESSE SERGE ET AL) 28 July 1992 (1992-07-28) column 2, line 27 -column 3, line 45 column 5 -column 7; examples 1,6,7 column 9, line 54 -column 10, line 8 | 1,3-13 |
| X | COUVREUR P, ET AL.: "Toxicity of polyalkylcyanoacrylate nanoparticles II: doxorubicin-loaded nanoparticles" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 71, no. 7, 1982, pages 790-792, XP000783921 ISSN 0022-3549 page 790, right-hand column, line 4 -page 791, left-hand column, line 12 | 1,3-13 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/03838

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| WO 9522963 | A | 31-08-1995 | AU 1947395 A | 11-09-1995 |
| | | | AU 9725898 A | 04-03-1999 |
| | | | CA 2184242 A | 31-08-1995 |
| | | | EP 0740548 A | 06-11-1996 |
| | | | HU 75469 A | 28-05-1997 |
| | | | JP 2930421 B | 03-08-1999 |
| | | | JP 9506109 T | 17-06-1997 |
| WO 9856361 | A | 17-12-1998 | AU 3176097 A | 30-12-1998 |
| DE 19745950 | A | 22-04-1999 | AU 1227299 A | 10-05-1999 |
| | | | WO 9920256 A | 29-04-1999 |
| US 5133908 | A | 28-07-1992 | FR 2608988 A | 01-07-1988 |
| | | | FR 2634397 A | 26-01-1990 |
| | | | AT 74024 T | 15-04-1992 |
| | | | CA 1292168 A | 19-11-1991 |
| | | | DE 3777796 A | 30-04-1992 |
| | | | EP 0275796 A | 27-07-1988 |
| | | | ES 2031151 T | 01-12-1990 |
| | | | GR 3004152 T | 31-03-1993 |
| | | | GR 3018122 T | 29-02-1996 |
| | | | JP 2739896 B | 15-04-1998 |
| | | | JP 63240936 A | 06-10-1988 |
| | | | US 5118528 A | 02-06-1992 |
| | | | AT 84710 T | 15-02-1993 |
| | | | EP 0349428 A | 03-01-1990 |
| | | | ES 2054052 T | 01-08-1994 |
| | | | GR 3007248 T | 30-07-1993 |
| | | | JP 1876957 C | 07-10-1994 |
| | | | JP 2149334 A | 07-06-1990 |
| | | | JP 6002224 B | 12-01-1994 |
| | | | KR 9614870 B | 21-10-1996 |

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number
WO 00/74658 A1

- (51) International Patent Classification⁷: **A61K 9/51**,
31/70, A61P 35/00
- (21) International Application Number: **PCT/EP99/03838**
- (22) International Filing Date: **2 June 1999 (02.06.1999)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (71) Applicant (for all designated States except US): **MEDINOVA MEDICAL CONSULTING GMBH [DE/DE];**
Zentrum für Neurowissenschaftliche Innovation u. Technologie (ZENIT), Leipziger-Strasse 44, D-39120 Magdeburg (DE).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **SABEL, Bernhard, A. [DE/DE];** Kronprinzessinnenweg 13, D-14109 Berlin (DE). **KREUTER, Jörg [DE/DE];** Georg-August-Zinn-Strasse 13, D-61350 Bad Homburg (DE). **GELPERINA, Svetlana [RU/RU];** Apartment No. 719, ul. Profsojuznaya, 113-3, Moscow, 117647 (RU).
- (54) Title: **USE OF DRUG-LOADED NANOPARTICLES FOR THE TREATMENT OF CANCERS**
- (57) Abstract: The present invention relates to the use of drug-loaded nanoparticles for preparing a medicament for the treatment of cancer, particularly for the treatment of cancer in the brain, even more particularly for the treatment of brain cancer in humans. The invention also relates to a process for the treatment of brain cancer, particularly for the treatment of brain cancer in humans by administering an effective amount of nanoparticles containing a substance which has effect in the cancer treatment or has immunosuppressive effects.
- (74) Agent: **KOEPE, Gerd, L.;** Blumbach, Kramer & Partner, Radeckestrasse 43, D-81245 München (DE).
- (81) Designated States (national): **AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW.**
- (84) Designated States (regional): **ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).**
- Published:
— With international search report.
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 00/74658 A1

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/EP 99/03838

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/51 A61K31/70 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO 95 22963 A (MEDINOVA MED CONSULTING GMBH) 31 August 1995 (1995-08-31) cited in the application the whole document in particular: page 6, line 10 -page 7 page 13, line 9 - line 11 | 1-14 |
| X | WO 98 56361 A (MEDINOVA MED CONSULTING GMBH ;SABEL BERNHARD A (DE); SCHROEDER ULR) 17 December 1998 (1998-12-17) cited in the application the whole document in particular: page 5, line 20 -page 9, line 5 page 15, line 1 - line 3 | 1-14 |
| | -/- | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "B" document member of the same patent family

Date of the actual completion of the international search

15 February 2000

Date of mailing of the international search report

24/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Epskamp, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/03838

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | DE 197 45 950 A (DDS DRUG DELIVERY SERVICE GES) 22 April 1999 (1999-04-22) page 3, line 27 -page 4, line 9 page 5, line 40 - line 45; examples 2,6; table 1 page 9, line 10 - line 26 claims 1-20 | 1-14 |
| X | RESZKA R, ET AL.: "Body distribution of free, liposomal and nanoparticle-associated mitoxantrone in B16-melanoma-bearing mice" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, 'Online! vol. 280, no. 1, 1997, pages 232-237, XP002129865 ISSN 0022-3565 Retrieved from the Internet: <URL:http://jpet.aspetjournals.org/cgi/rep rint/280/1/232> 'retrieved on 2000-02-07! page 233, line 31 - line 49 page 233, line 57 -page 234, line 21 page 236, line 12 - line 27; figures 1-6; table 1 | 1,3-13 |
| X | US 5 133 908 A (STAINMESSE SERGE ET AL) 28 July 1992 (1992-07-28) column 2, line 27 -column 3, line 45 column 5 -column 7; examples 1,6,7 column 9, line 54 -column 10, line 8 | 1,3-13 |
| X | COUVREUR P, ET AL.: "Toxicity of polyalkylcyanoacrylate nanoparticles II: doxorubicin-loaded nanoparticles" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 71, no. 7, 1982, pages 790-792, XP000783921 ISSN 0022-3549 page 790, right-hand column, line 4 -page 791, left-hand column, line 12 | 1,3-13 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/ 03838

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 12-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/03838

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|---|--|
| WO 9522963 A | 31-08-1995 | AU 1947395 A AU 9725898 A CA 2184242 A EP 0740548 A HU 75469 A JP 2930421 B JP 9506109 T | 11-09-1995 04-03-1999 31-08-1995 06-11-1996 28-05-1997 03-08-1999 17-06-1997 |
| WO 9856361 A | 17-12-1998 | AU 3176097 A | 30-12-1998 |
| DE 19745950 A | 22-04-1999 | AU 1227299 A WO 9920256 A | 10-05-1999 29-04-1999 |
| US 5133908 A | 28-07-1992 | FR 2608988 A FR 2634397 A AT 74024 T CA 1292168 A DE 3777796 A EP 0275796 A ES 2031151 T GR 3004152 T GR 3018122 T JP 2739896 B JP 63240936 A US 5118528 A AT 84710 T EP 0349428 A ES 2054052 T GR 3007248 T JP 1876957 C JP 2149334 A JP 6002224 B KR 9614870 B | 01-07-1988 26-01-1990 15-04-1992 19-11-1991 30-04-1992 27-07-1988 01-12-1990 31-03-1993 29-02-1996 15-04-1998 06-10-1988 02-06-1992 15-02-1993 03-01-1990 01-08-1994 30-07-1993 07-10-1994 07-06-1990 12-01-1994 21-10-1996 |